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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	14

DATE MAILED: 04/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
10/006,430	GRAHAM ET AL.
Examiner	**Art Unit**
Mary Schmidt	1635

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,11,12 and 14-20* is/are rejected.

7)☒ Claim(s) *3-10 and 13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3
4)☐ Interview Summary (PTO-413) Paper No(s). _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☒ Other: Accession.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense to CD81 use in cells in culture (*in vitro*), does not reasonably provide enablement for any nucleic acid sequence 8-50 bases which hybridizes to any potential sequence considered CD81 for use in whole organisms as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 15-20 are drawn to methods of use of antisense sequences to CD81 which read on use in whole organisms. In the instant case, the claims read broadly on administration of an antisense inhibitor in any cell, therefore the whole organism included. While the specification teaches cell culture inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery.

There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation,

and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more

efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on

whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 2, 11, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by GenEMbl database AX004402/c (Aug. 24, 2000).

Claims 1, 2, 11, 12 and 14 are drawn to compositions comprising 8 to 50 nucleobases targeted to CD81 including antisense compositions. Claims 12 and 14 are included in the instant art rejection since the limitation therein "pharmaceutically acceptable carrier or diluent" is not considered to breath new life and meaning into what appears to be a claim to an otherwise known prior art nucleic acid, absent evidence to the contrary.

GenEMbl database AX004402/c teaches a sequence of 41 bases which has bases 6-20 of instant SEQ ID NO: 30. Absent evidence to the contrary, the sequence disclosed in the prior art would have an expectation to function as an antisense to CD81 due to the 75% homology with instant SEQ ID NO:30. Note also MPEP 2112.01 which states that "if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present."GenEMbl database AX004402/c teaches an oligonucleotide having the claimed structure, and thus reads on the instant invention as claimed.

5. Claims 1, 2, 11, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by EST database AZ465883 (apr. 5, 2001).

Claims 1, 2, 11, 12 and 14 are drawn to compositions comprising 8 to 50 nucleobases targeted to CD81 including antisense compositions. Claims 12 and 14 are included in the instant art rejection since the limitation therein "pharmaceutically acceptable carrier or diluent" is not considered to breath new life and meaning into what appears to be a claim to an otherwise known prior art nucleic acid, absent evidence to the contrary.

EST database AZ465883 teaches a sequence of 19 bases which has bases 5-17 of instant SEQ ID NO: 49. Absent evidence to the contrary, the sequence disclosed in the prior art would have an expectation to function as an antisense to CD81 due to the 65% homology with instant SEQ ID NO:49. Note also MPEP 2112.01 which states that "if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." EST database AZ465883 teaches an oligonucleotide having the claimed structure, and thus reads on the instant invention as claimed.

6. Claims 1, 2, 11, 12 and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by GenEmbl database AX174772 (Jul. 3, 2001).

Claims 1, 2, 3, 11, 12 and 14 are drawn to compositions comprising 8 to 50 nucleobases targeted to CD81 including antisense compositions. Claims 12 and 14 are included in the instant art rejection since the limitation therein "pharmaceutically acceptable carrier or diluent" is not considered to breath new life and meaning into what appears to be a claim to an otherwise known prior art nucleic acid, absent evidence to the contrary.

GenEmbl database AX174772 teaches a sequence of 50 bases which has bases 2-14 of instant SEQ ID NO: 51. Absent evidence to the contrary, the sequence disclosed in the prior art would have an expectation to function as an antisense to CD81 due to the 65% homology with instant SEQ ID NO:51. Note also MPEP 2112.01 which states that "if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present."GenEmbl database AX174772 teaches an oligonucleotide having the claimed structure, and thus reads on the instant invention as claimed.

7. Claims 1, 2, 11, 12 and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by GenEmbl database AX174772 (Jul. 3, 2001).

Claims 1, 2, 11, 12 and 14 are drawn to compositions comprising 8 to 50 nucleobases targeted to CD81 including antisense compositions. Claims 12 and 14 are included in the instant art rejection since the limitation therein "pharmaceutically acceptable carrier or diluent" is not considered to breath new life and meaning into what appears to be a claim to an otherwise known prior art nucleic acid, absent evidence to the contrary.

GenEmbl database AX174772 teaches a sequence of 18 bases which has bases 7-19 of instant SEQ ID NO: 52. Absent evidence to the contrary, the sequence disclosed in the prior art would have an expectation to function as an antisense to CD81 due to the 65% homology with instant SEQ ID NO:52. Note also MPEP 2112.01 which states that "if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily

present." GenEmbl database AX174772 teaches an oligonucleotide having the claimed structure, and thus reads on the instant invention as claimed.

8. Claims 1, 2, 11, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by GenEmbl database AR026492 (Sept. 29, 1999).

Claims 1, 2, 11, 12 and 14 are drawn to compositions comprising 8 to 50 nucleobases targeted to CD81 including antisense compositions. Claims 12 and 14 are included in the instant art rejection since the limitation therein "pharmaceutically acceptable carrier or diluent" is not considered to breath new life and meaning into what appears to be a claim to an otherwise known prior art nucleic acid, absent evidence to the contrary.

GenEmbl database AR026492 teaches a sequence of 18 bases which has bases 1-13 of instant SEQ ID NO: 54. Absent evidence to the contrary, the sequence disclosed in the prior art would have an expectation to function as an antisense to CD81 due to the 65% homology with instant SEQ ID NO:54. Note also MPEP 2112.01 which states that "if the prior art teaches the identical chemical structure, the GenEmbl database AR026492 teaches an oligonucleotide having the claimed structure, and thus reads on the instant invention as claimed.

9. Claims 1, 2, 11, 12 and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by GenEmbl database AB069260 (Aug. 8, 2001).

Claims 1, 2, 11, 12 and 14 are drawn to compositions comprising 8 to 50 nucleobases targeted to CD81 including antisense compositions. Claims 12 and 14 are included in the instant art rejection since the limitation therein "pharmaceutically acceptable carrier or diluent" is not considered to breath new life and meaning into what appears to be a claim to an otherwise known prior art nucleic acid, absent evidence to the contrary.

GenEmbl database AB069260 teaches a sequence of 18 bases which has bases 7-19 of instant SEQ ID NO: 60. Absent evidence to the contrary, the sequence disclosed in the prior art would have an expectation to function as an antisense to CD81 due to the 65% homology with instant SEQ ID NO:60. Note also MPEP 2112.01 which states that "if the prior art teaches the identical chemical structure, the GenEmbl database AB069260 teaches an oligonucleotide having the claimed structure, and thus reads on the instant invention as claimed.

10. Claims 1, 2, 11, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by GenEmbl database AR040450 (Sept. 29, 1999).

Claims 1, 2, 11, 12 and 14 are drawn to compositions comprising 8 to 50 nucleobases targeted to CD81 including antisense compositions. Claims 12 and 14 are included in the instant art rejection since the limitation therein "pharmaceutically acceptable carrier or diluent" is not considered to breath new life and meaning into what appears to be a claim to an otherwise known prior art nucleic acid, absent evidence to the contrary.

GenEmbl database AR040450 teaches a sequence of 27 bases which has bases 1-14 of instant SEQ ID NO: 61. Absent evidence to the contrary, the sequence disclosed in the prior art would have an expectation to function as an antisense to CD81 due to the 70% homology with instant SEQ ID NO:61. Note also MPEP 2112.01 which states that "if the prior art teaches the identical chemical structure, the GenEmbl database AR040450 teaches an oligonucleotide having the claimed structure, and thus reads on the instant invention as claimed.

11. Claims 1, 2, 11, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by GenEmbl database I76404 (Apr. 3, 1998).

Claims 1, 2, 11, 12 and 14 are drawn to compositions comprising 8 to 50 nucleobases targeted to CD81 including antisense compositions. Claims 12 and 14 are included in the instant art rejection since the limitation therein "pharmaceutically acceptable carrier or diluent" is not considered to breath new life and meaning into what appears to be a claim to an otherwise known prior art nucleic acid, absent evidence to the contrary.

GenEmbl database I76404 teaches a sequence of 23 bases which has bases 7-19 of instant SEQ ID NO: 63. Absent evidence to the contrary, the sequence disclosed in the prior art would have an expectation to function as an antisense to CD81 due to the 65% homology with instant SEQ ID NO:63. Note also MPEP 2112.01 which states that "if the prior art teaches the identical chemical structure, the GenEmbl database I76404 teaches an oligonucleotide having the claimed structure, and thus reads on the instant invention as claimed.

12. Claims 1, 2, 11, 12 and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by EST database AZ941495 (Apr. 26, 2001).

Claims 1, 2, 11, 12 and 14 are drawn to compositions comprising 8 to 50 nucleobases targeted to CD81 including antisense compositions. Claims 12 and 14 are included in the instant art rejection since the limitation therein "pharmaceutically acceptable carrier or diluent" is not considered to breath new life and meaning into what appears to be a claim to an otherwise known prior art nucleic acid, absent evidence to the contrary.

EST database AZ941495 teaches a sequence of 42 bases which has bases 4-16 of instant SEQ ID NO: 68. Absent evidence to the contrary, the sequence disclosed in the prior art would have an expectation to function as an antisense to CD81 due to the 65% homology with instant SEQ ID NO:68. Note also MPEP 2112.01 which states that "if the prior art teaches the identical chemical structure, the EST database AZ941495 teaches an oligonucleotide having the claimed structure, and thus reads on the instant invention as claimed.

13. Claims 1, 2, 11, 12 and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by GenEmbl database AX090066 (Mar. 21, 2001).

Claims 1, 2, 11, 12 and 14 are drawn to compositions comprising 8 to 50 nucleobases targeted to CD81 including antisense compositions. Claims 12 and 14 are included in the instant art rejection since the limitation therein "pharmaceutically acceptable carrier or diluent" is not

considered to breath new life and meaning into what appears to be a claim to an otherwise known prior art nucleic acid, absent evidence to the contrary.

GenEmbl database AX090066 teaches a sequence of 26 bases which has bases 1-13 of instant SEQ ID NO: 71. Absent evidence to the contrary, the sequence disclosed in the prior art would have an expectation to function as an antisense to CD81 due to the 65% homology with instant SEQ ID NO:71. Note also MPEP 2112.01 which states that "if the prior art teaches the identical chemical structure, the GenEmbl database AX090066 teaches an oligonucleotide having the claimed structure, and thus reads on the instant invention as claimed.

14. Claims 1, 2, 11, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by EST database AZ493934 (Oct. 5, 2000).

Claims 1, 2, 11, 12 and 14 are drawn to compositions comprising 8 to 50 nucleobases targeted to CD81 including antisense compositions. Claims 12 and 14 are included in the instant art rejection since the limitation therein "pharmaceutically acceptable carrier or diluent" is not considered to breath new life and meaning into what appears to be a claim to an otherwise known prior art nucleic acid, absent evidence to the contrary.

EST database AZ493934 teaches a sequence of 39 bases which has bases 1-13 of instant SEQ ID NO: 75. Absent evidence to the contrary, the sequence disclosed in the prior art would have an expectation to function as an antisense to CD81 due to the 65% homology with instant SEQ ID NO:75. Note also MPEP 2112.01 which states that "if the prior art teaches the identical

chemical structure, the EST database AZ493934 teaches an oligonucleotide having the claimed structure, and thus reads on the instant invention as claimed.

15. Claims 1, 2, 11, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by GenEmbl database I07146 (Dec. 2, 1994).

Claims 1, 2, 11, 12 and 14 are drawn to compositions comprising 8 to 50 nucleobases targeted to CD81 including antisense compositions. Claims 12 and 14 are included in the instant art rejection since the limitation therein "pharmaceutically acceptable carrier or diluent" is not considered to breath new life and meaning into what appears to be a claim to an otherwise known prior art nucleic acid, absent evidence to the contrary.

GenEmbl database I07146 teaches a sequence of 32 bases which has bases 5-17 of instant SEQ ID NO: 76. Absent evidence to the contrary, the sequence disclosed in the prior art would have an expectation to function as an antisense to CD81 due to the 65% homology with instant SEQ ID NO:76. Note also MPEP 2112.01 which states that "if the prior art teaches the identical chemical structure, the GenEmbl database I07146 teaches an oligonucleotide having the claimed structure, and thus reads on the instant invention as claimed.

16. Claims 1, 2, 11, 12 and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by GenEmbl database AB069260 (Aug. 8, 2001).

Claims 1, 2, 11, 12 and 14 are drawn to compositions comprising 8 to 50 nucleobases targeted to CD81 including antisense compositions. Claims 12 and 14 are included in the instant

art rejection since the limitation therein "pharmaceutically acceptable carrier or diluent" is not considered to breath new life and meaning into what appears to be a claim to an otherwise known prior art nucleic acid, absent evidence to the contrary.

GenEmbl database AB069260 teaches a sequence of 18 bases which has bases 5-17 of instant SEQ ID NO: 88. Absent evidence to the contrary, the sequence disclosed in the prior art would have an expectation to function as an antisense to CD81 due to the 65% homology with instant SEQ ID NO:88. Note also MPEP 2112.01 which states that "if the prior art teaches the identical chemical structure, the GenEmbl database AB069260 teaches an oligonucleotide having the claimed structure, and thus reads on the instant invention as claimed.

17. Claims 3-10 and 13 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The art does not teach nor fairly suggest nucleic acid compositions comprising the claimed SEQ ID NOS. in claim 3 nor the specific limitations in claims 4-10 and 13 as applied to the nucleic acids taught in the 35 U.S.C. 102 rejections above.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
April 19, 2002

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